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TITLE: "The Johns Hopkins RTR Consortium: A Collaborative Approach to Advance Translational Science and Standardize Clinical Monitoring of Restorative Transplantation"

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13. SUPPLEMENTARY NOTES							
14. ABSTRACT The overall goal for the Johns Hopkins RTR Consortium is to advance translational research of the most clinically pertinent issues of Restorative Transplantation through a multidisciplinary collaboration among highly experienced and accomplished partners. The Consortium has thus assembled three complimentary, multidisciplinary research projects from Johns Hopkins, Massachusetts General Hospital and University of Pittsburgh. Each of the individual projects has made significant progress during this reporting period. The Initiating Site through their coordinated efforts has facilitated that all projects are mostly on track with the proposed statements of work. The group has met all Major Tasks for Year 2, in particular we have assisted sites with ACURO and HRPO submissions, contacted sites to remind them of upcoming Quarterly Report deadlines, Collected and Reviewed Quarterly Reports and held update calls to discuss progress among project leaders.							
15. SUBJECT TERMS Vascularized Composite Allotransplantation, Immunoregulation, Tolerance Rejection, Ischemia Reperfusion Cell based Therapy, Large animal models, Allograft, Hand Transplantation ,Face Transplantation							
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1. INTRODUCTION

Restorative Transplantation has emerged as a new modality to restore both function and form following devastating injuries to the face and upper extremities in a way not previously possible. Despite initial success, great challenges remain in ameliorating long-term immunosuppression, understanding acute and chronic rejection, and optimizing immune monitoring and perioperative protocols. As the field of Restorative Transplantation matures, significant opportunities are emerging for transplant researchers and clinicians to capitalize on the unique features of VCA, glean from advances and experience in solid organ transplantation (SOT), and achieve genuine progress in transplant outcome and patient safety. **The Johns Hopkins RTR Consortium** has thus *assembled some of the world's most renowned scientists, researchers, and surgeons in vascularized composite allotransplantation (VCA) research to address some of the most relevant and pressing research areas in reconstructive transplantation.*

The **overall goal** for the Johns Hopkins RTR Consortium is to advance translational research of the most clinically pertinent issues of Restorative Transplantation through a multidisciplinary collaboration among highly experienced and accomplished partners. The **central hypothesis** is that the maturing field of Restorative Transplantation will benefit the most from the establishment of a multi-institutional, multi-disciplinary collaborative consortium that builds on knowledge and experience derived from the study of SOT to address the unique challenges and opportunities presented in this new field.



2. KEYWORDS

Vascularized Composite Allograft
Immunoregulation
Tolerance
Rejection
Ischemia Reperfusion
Cell based Therapy
Large animal models
Allograft
Hand Transplantation
Face Transplantation

3. ACCOMPLISHMENTS

The Initiating Site has met all Major Tasks for Year 3 as outlined in the Statement of Work. In particular, we have assisted sites with ACURO and HRPO submissions, No Cost Extensions (NCE), contacted sites to remind them of upcoming Quarterly Report deadlines, Collected and Reviewed Quarterly and Annual Reports and held update calls to discuss progress among project leaders.

The accomplishments for each of the individual projects are outlined below:

Johns Hopkins University (MR120034P10)

During the current reporting period the group continue to study a belatacept-based protocol to enable calcineurin inhibitor (CNI) minimization/avoidance (Aim 1) after heterotopic swine hind-limb allotransplantation across a full SLA mismatch and furthermore set out to examine the efficacy of transitioning to belatacept (CTLA4-Ig) maintenance therapy from a calcineurin inhibitor based immunosuppression regimen (Aim 2) and to compare immunomodulatory donor BM infusion to BM transplantation with establishment of durable mixed chimerism for induction tolerance and/or VCA survival on CNI free immunosuppression using a belatacept-based regimen (Aim 3).

Achievements:

- Unexpected long-term graft survival of animals receiving a VCA combined with short-term immunosuppression, i.e. high-dose tacrolimus, yielded scientifically promising results. Graft survival significantly exceeded our expectations resulting in long-term/indefinite graft survival in some of the experimental groups. Although to date *in-vivo* experiments have largely been completed, several of these most valuable animals are still ongoing with functioning rejection-free grafts, which we will continue monitor. The detailed data outlined in the annual report highlights the powerful immunomodulatory contributions of grafts containing vascularized bone

- marrow and indicate that these grafts may be more conducive to immunosuppression sparing protocols as well as tolerance induction.
- The addition of CTLA4-Ig to subtherapeutic CNI does not appear to be able to prevent graft rejection. Tolerance of VCA containing a vascularized bone component may be achieved with a conditioning regimen of non-myeloablative irradiation and peritransplant tacrolimus. In addition, unexpected results have shown that indefinite graft survival can be achieved subsequent to induction and transient high-dose tacrolimus monotherapy in VCAs containing a vascularized bone marrow component or with additional donor bone marrow cell infusion. This could allow the development of alternative protocols devoid of the well-known and documented toxicities and side effects of CNIs, which are currently hampering broader application of these life changing reconstructive modalities.. Additional clinical follow-up and *in vitro* assays need to be performed to characterize this finding.
 - Optimization of CFSE-Mixed Lymphocytic Reaction (CFSE-MLR) assays has represented a challenge but was achieved by magnetic separation of CD4+ and CD8+ populations within peripheral blood mononuclear cells (PBMCs) and by labeling of the stimulator cells.

Progress against SOW:

- As detailed in the Annual Report
- The investigators were not able to complete all the experimental groups investigating the tolerogenic effects of combined BMI and peri-transplant CTLA4-Ig (traditional and intensified) due to initial animal deaths due to complications of the regimen that required repeat transplants.

Challenges:

- In-vivo* experiments have been performed according to the statement of work. However, minimal delays in animal availability from the breeder at Massachusetts General Hospital (MGH) have accumulated and contributed to delayed completion of *in-vivo* as well as associated *in-vitro* experiments.
- In light of the promising results obtained as stated in the detailed annual report and due to the delay in availability of animals, the investigators have submitted a NCE for this project. The additional time will be utilized to finalize the histology and immunohistochemistry data to determine graft infiltrating T cell phenotypes, immune phenotyping PBMCs using FACS and analysis of donor specific antibodies. These additional experiments and data analysis will be performed in conjunction with the collaborators at MGH as outlined by the SOW over the next year.
- The CFSE-MLR assays represented a prolonged challenge due to the inability to consistently obtain adequate stimulation of responder cells. A systematic and analytical approach was undertaken to allow optimization of the assay, which required numerous modifications to the original protocol.
- Preliminary pathology findings have identified radiation-related cardiac injury as the possible contributor to the clinical outcome of two animals in group VIII. The

development and use of a radiation-free protocol is therefore warranted in the future to reduce induction regimen-related mortality.

Massachusetts General Hospital (MR120034P5)

Achievements:

- Successfully modified delay period on immunosuppression from 4 to 2 months to avoid lethal complications such as PTLD
- Demonstrated that acute skin rejection episodes develop in a predictable and temporal sequence with clinical, histological and supporting *in vitro* analysis; also showed that prompt diagnosis and treatment with steroid bolus and gradual taper can not only reverse the episode but prevent progression/recurrence up to POD 60
- Achieved short- to medium-term complete immunosuppression withdrawal but did not achieve long-term tolerance due to the failure of tolerance induction (i.e. no mixed chimerism generated)
- Showed that long-term survival, even with reduced immunosuppression, does not negate the spectre of chronic rejection, which develops from deeper tissues

Progress against SOW:

- As detailed in the Annual Report
- Was not able to complete the experimental groups investigating CTLA4-Ig/rapamycin and CTLA4-Ig/rapamycin/anti-IL-6R as an alternative strategy to improve *in vivo* Treg upregulation due to the run of technical failures in the hand transplant model initially, and the ever-increasing costs of ATGAM

Challenges:

- Strategies to avoid the development of PTLD are required so that longer term follow-up can be achieved even if mixed chimerism cannot be generated because this may lend further insight into the development of chronic rejection and/or salvage therapies required should tolerance induction fail. In turn, this will help inform patients clinically on the risks and sequelae of failed tolerance induction
- Strategies to promote engraftment of donor bone marrow cells following infusion so as to achieve the greatest likelihood of generating mixed chimerism and thus, experimental success. Perhaps intra-arterial administration would be preferable to avoid the first-pass effect of pulmonary sequestration which further reduces the quantity of viable hematopoietic stem cells from donor bone marrow

University of Pittsburgh (MR120034P4)

Achievements:

1. The MP/HBOC system provided low pressures (50-55 mmHg), low flows (20-80 ml/min) and full oxygenation ($\text{FiO}_2=60\% @ 400\text{ml/min}$) to the VRAM grafts
2. The MP/HBOC system stabilized the perfusate's pH (7.55-7.6) while keeping lactate levels under 4mmol/L (Figure 3). In spite the prolonged period of perfusion (14 hours), there was no need to proceed with additional NaHCO_3 infusions as seen in previous similar experiments with different MP systems
3. Myoglobin blood levels were significantly higher in CSP flap recipients, showing the magnitude of the IRIs seen in the current standard of care for tissue preservation when compared to the MP/HBOC system
4. Early damage on the CSP grafts was clearly detected within the initial samples (4 and 8 hours). The presence of early hypercontracted sarcomeres (contraction bands - CB) and frequent sarcolemmal ruptures that gave rise to the term "contraction band necrosis" were observed in the sarcomeres, which were subsequently followed by moderate to severe IRI in the CSP flaps *in vivo*. CB are thick, irregular, transverse eosinophilic bands in necrotic myocytes. CB occur whenever there is a massive influx of Ca^{++} into the myocytes. The bands are small groups of hypercontracted and disorganized sarcomeres with thickened Z lines. The sarcolemma is disrupted and the mitochondria located between the CB swell. The CB became more prominent after reperfusion and led into extensive necrosis within the CSP group. Adiponecrosis and skin necrosis were also significantly higher in the CSP group.
5. The skin portion was mildly affected on both groups initially indicating some initial ischemia reperfusion injuries (IRI) as a result of the transplant process. The control CSP group progressed towards further necrosis and ischemic ulcerations of the skin, whereas the study MP group stabilized. There were significant differences between the 2 groups (CSP and MP) when overall viability and full thickness tissue integrity was assessed for IRI. The MP group had mild signs of IRI in the 3 segments of the graft (e.g. skin, adipose tissue and muscle). The CSP group had moderate to severe signs of IRI within the 3 segments of the VRAM grafts. There were also signs of considerable irreversible damage within the vascular endothelial cells leading to further apoptosis and necrosis within the adipose and muscular tissues in the CSP group. The presence of perivascular edema, red blood cell extravasation, leukocyte adhesion and infiltration, intraluminal thrombi of microvasculature and progressive loss of the endothelial cell layer in mid-size vessels were also observed in the CSP group. The initial endothelial cell dysfunction apparently led to further vascular leakage in the CSP group. Additional macrophage and eosinophilic infiltration were detected in the CSP group. Nuclear changes (e.g. pyknosis, karyorrhexis and karyolysis) were further observed as signs of apoptosis and necrosis within the muscular layer in the CSP group. Furthermore, fiber disruption, loss of striation and additional decomposition of both the endomysium and epimysium were clearly noticed in the CSP group. These classic histological inflammatory features of significant IRI injuries were rarely noticed in the MP group, showing the beneficial role of effective oxygenation as a way to avoid ischemic injuries during VRAM graft preservation. The degree of apoptosis and necrosis was significantly higher in the CSP group than the MP group, where

intraseptal lymphocyte infiltration and progressive muscle fiber atrophy is also seen. Cell debris (both from the resident cell populations and from infiltrating leukocytes); proteinaceous fluid containing fibrin, fewer macrophages and occasional lymphocytes and/or plasma cells are seen in the CSP. None of these changes were seen in the MP/HBOC group.

6. The VRAM grafts in the MP system sustained an intact energetic metabolism fueled by glucose over the 14 hour period of preservation when compared to the CSP group. MP sustained normal skeletal muscle glycolysis as evident by higher: glucose 6-phosphate (\uparrow 23 fold, $p=0.01$), fructose-6-phosphate (\uparrow 12 fold, $p=0.03$), and phosphoenolpyruvate (\uparrow 8 fold, $p=0.03$). Nucleic acid synthesis was significantly higher in the MP flaps: cysteine (\uparrow 3.88 fold, $p=0.02$), ribose (\uparrow 22 fold, $p<0.001$), ribonate (\uparrow 37 fold, $p<0.001$), and ribitol (\uparrow 10.5 fold, $p<0.001$). MP led to significantly higher levels of reactive oxygen species (ROS) scavengers in the VCAs: glutathione-cysteine disulfide (\uparrow 5.6 fold, $p=0.01$) and N-acetylcysteine (\uparrow 40 fold, $p=0.007$).

7. SNMP provided sufficient energy precursors and metabolites: adenine (\uparrow 129 fold, $p=0.002$), cAMP (\uparrow 3.7 fold, $p=0.02$), AMP (\uparrow 3.2 fold, $p=0.01$) and 3'-AMP (\uparrow 2.3 fold, $p=0.01$). CSP grafts faced extensive amino acid metabolism dysregulation as suggested by significantly higher levels of: N⁶-succinyladenosine ($p<0.01$), valine ($p<0.01$), 2-methylbutyrylcarnitine ($p=0.01$), 3-hydroxyisobutyrate ($p=0.01$), and ethylmalonate ($p=0.009$) tissue levels. Glycogen reserves were higher in the MP group. There was adequate glucose supply in the MP and no signs on glycogen breakdown. The pentose metabolites were significantly higher in the MP group, showing a higher anabolic state when compared to the CSP group. The CSP group appeared to have a sustained catabolic state when compared to the MP group. There were signs of higher production of nucleotides and nucleic acids precursors in the MP.

8. As previously seen in our experience with liver allografts under the MP/HBOC system, there was a significant (30 fold higher) increase in the metabolic pathways related to cell regeneration once oxygenation was effectively provided ex-vivo during preservation. There were signs of higher production of aromatic amino acids in the MP group when compared to the CSP group. The MP/HBOC system provided more effective anti-oxidant pathways when compared to the CSP group.

9. There were higher levels of end-products from oxidized stress in the MP group, which can be seen as an indirect sign of lower stress from less significant IRIs when compared to the CSP group. Contrary to our previous experience with livers, the VRAM grafts under the MP/HBOC system showed lower fatty acid β -oxidation when compared to the CSP group. This means a lower of fatty acids into the mitochondria as a source of fuel. This also favors our initial findings regarding the preferential pathway for glucose as the primary source of energy in striated muscles. Further analysis of the purine metabolism (adenine components) showed indirect signs of higher ATP production in the MP group when compared to the CSP. The adenine family has a variety of roles in cellular respiration and protein synthesis. There were higher levels of cAMP in the MP group, showing higher ATP production in this group. AMP is used as a monomer in RNA synthesis. The

cAMP as a derivative of ATP has a significant role in signal transduction. SNMP increased fatty acids (FAs) Ω -oxidation pathway as evident by significantly higher tissue levels of dicarboxylic FAs: 2-hydroxyglutarate (\uparrow 4.8 folds, p=0.02), adipate (\uparrow 5.55 folds, p=0.003), and 2-hydroxyadipate (\uparrow 2.5 folds, p=0.01). Reduction of β -oxidation was evident by substantial increase in the levels of acyl-carnitine metabolites in the SNMP/HBOC grafts: cis-4-decenoyl carnitine (\uparrow 8 folds, p=0.04), laurylcarnitine (\uparrow 8.3 folds, p=0.02), oleoylcarnitine (\uparrow 9.5 folds, p=0.01), myristoleoylcarnitine (\uparrow 22 folds, p=0.006), and adipoylcarnitine (\uparrow 7 folds, p<0.001). This was mirrored by significantly higher levels of end-products of β -oxidation pathway in the CSP group as shown by 4-hydroxybutyrate (p<0.01). Cellular membrane integrity was well preserved histologically and further evidenced by significantly higher levels of phospholipids in the SNMP/HBOC group: oleoylcholine (\uparrow 5 folds, p<0.01) and choline (\uparrow 3 folds, p=0.01). In addition, early signs of myopathy were observed with significantly higher tissue levels of butyryl-carnitine (p=0.04) in the CSP grafts, which were further corroborated by histopathologic analysis.

Conclusions:

1. The MP/HBOC system can effectively preserve VRAM allografts when compared to CSP. MP significantly mitigates IRI, which was manifested earlier within the first 4 hours in the CSP group.
2. Effective *ex-vivo* oxygenation with the MP/HBOC system decreases post-transplant inflammation in skeletal muscle fibers and upregulates regenerative metabolic pathways driving early recovery from IRI. There is a similar up-regulation of TNF- α in the CSP group, which is similar to our previous data obtained in liver allografts after a period of 9 hours of preservation.
3. Effective *ex-vivo* oxygenation with the MP/HBOC system avoids the early (hours) formation of hypercontracted sarcomeres (CB) and the subsequent development (days) of myofiber necrosis, myopathic changes, edema and hemorrhage seen extensively in CSP as the current standard of care.
4. The significant IRI observed in the CSP group yielded a significant hypereosinophilic sarcomere degeneration leading into irreversible loss of muscle fibers, followed by progressive granulomatous inflammation accompanied by the infiltration of large, activated macrophages, epithelioid macrophages and multinucleated giant cells, leading into terminal mineralization and complete loss of muscle mass.
5. Metabolic precursors of nucleotide synthesis were significantly upregulated in the MP/HBOC group. These precursors appear to be implicated in a strong regenerative response elicited by effective oxygenation of skeletal muscle, which also has a positive impact in energy utilization and ROS scavengers.
6. The MP/HBOC also promoted effective *ex vivo* oxygenation and shifted skeletal muscle metabolic profile from β -oxidation towards Ω -oxidation during VCA preservation when compared to the prolonged anoxia under hypothermic conditions

induced by CSP. This can be interpreted as a sign of mitochondrial dysfunction experienced by the CSP group. In fact, Ω -oxidation is linked to balanced redox state and less oxidative damage during stressful conditions induced by these experiments.

7. In contrast, CSP appears to increase a reactive skeletal muscle β -oxidation pathway, which leads into oxidative damage and disintegration of cellular membranes when prolonged hypothermia, anoxia, and limited glucose supply is imposed. Contrary to the CSP group, MP/HBOC protects skeletal muscle against early graft myopathy. These complex metabolic features seen in the both the muscle and adipose tissue were extensively corroborated by the serial histological findings, revealing in a close analogy the same protective role exerted by effective ex-vivo oxygenation documented extensively in our previous liver experiments.

a. What were the major goals of the project?

The **overall goal** for the Johns Hopkins RTR Consortium is to advance translational research of the most clinically pertinent issues of Restorative Transplantation through a multidisciplinary collaboration among highly experienced and accomplished partners.

b. What was accomplished under these goals?

Each of the individual projects has made significant progress as detailed above. The Initiating Site through their coordinated efforts has facilitated that all projects are mostly on track with the proposed statements of work. We have requested No Cost Extensions for two of the three projects. University of Pittsburgh is completing final data analysis at this time but has completed the experimental work. Massachusetts General Hospital and Johns Hopkins University will be completing the proposed work over the next period of performance.

c. What opportunities for training and professional development has the project provided?

Nothing to Report.

d. How were the results disseminated to communities of interest?

Nothing to Report

e. What do you plan to do during the next reporting period to accomplish the goals?

We will continue our coordinated efforts and increase the frequency of project leader conference calls to ensure timely completion of the tasks as outlined in the statement of work.

4. IMPACT:

- a. **What was the impact on the development of the principal discipline(s) of the project?**

Nothing to report

- b. **What was the impact on other disciplines?**

Nothing to report

- c. **What was the impact on technology transfer?**

Nothing to report

- d. **What was the impact on society beyond science and technology?**

Nothing to report

CHANGES/PROBLEMS:

- a. **Changes in approach and reasons for change**

Nothing to report.

- b. **Actual or anticipated problems or delays and actions or plans to resolve them**

Nothing to report.

- c. **Changes that had a significant impact on expenditures**

Nothing to report.

- d. **Significant changes in use or care of human subjects, vertebrate animals, biohazards, and/or select agents**

Nothing to report.

- d. **Significant changes in use or care of human subjects**

Nothing to report.

- e. **Significant changes in use or care of vertebrate animals.**

Nothing to report.

f. Significant changes in use of biohazards and/or select agents

Nothing to report.

5. PRODUCTS

Nothing to report.

6. PARTICIPANTS & OTHER COLLABORATING ORGANIZATIONS

a. What individuals have worked on the project?

Name: W. P. Andrew Lee

Project Role: Principal Investigator

Nearest Person Month Worked: 5% (0.6 calendar months)

Contribution to Project:

Name: Gerald Brandacher

Project Role: Co-Investigator

Nearest Person Month Worked: 5% (0.6 calendar months)

Contribution to Project:

Name: Rochelle Smith

Project Role: Assistant Grant Administrator

Nearest Person Month Worked: 40% (4.8 months)

Contribution to Project: Rochelle Smith drafts reminder emails to send to each site prior to report submission deadlines, coordinates with the PIs to obtain updated information, maintains financial records, and oversees project progress with the Scientific Director and PI.

b. Has there been a change in the active other support of the PD/PI(s) or senior/key personnel since the last reporting period?

Nothing to Report

c. Partnering Organization

Johns Hopkins University (MR120034P10)

Gerald Brandacher, MD

Johns Hopkins University

Baltimore, Maryland

Massachusetts General Hospital (MR120034P5)

Curtis L. Cetrulo, MD

Massachusetts General Hospital

Boston, Massachusetts

University of Pittsburgh (MR120034P4)

Paulo Fontes, MD

University of Pittsburgh

Pittsburgh, PA

d. SPECIAL REPORTING REQUIREMENTS

- a. **QUAD CHARTS:** Attached.

e. APPENDICES

Nothing to Report.

The Johns Hopkins RTR Consortium: A Collaborative Approach to Advance Translational Science and Standardize Clinical Monitoring of Restorative Transplantation

MR120034, Restorative Transplantation Research

Award Number: W81XWH-13-2-0059

PI: W. P. Andrew Lee, M.D.

Org: Johns Hopkins University, School of Medicine Award Amount: \$286,298

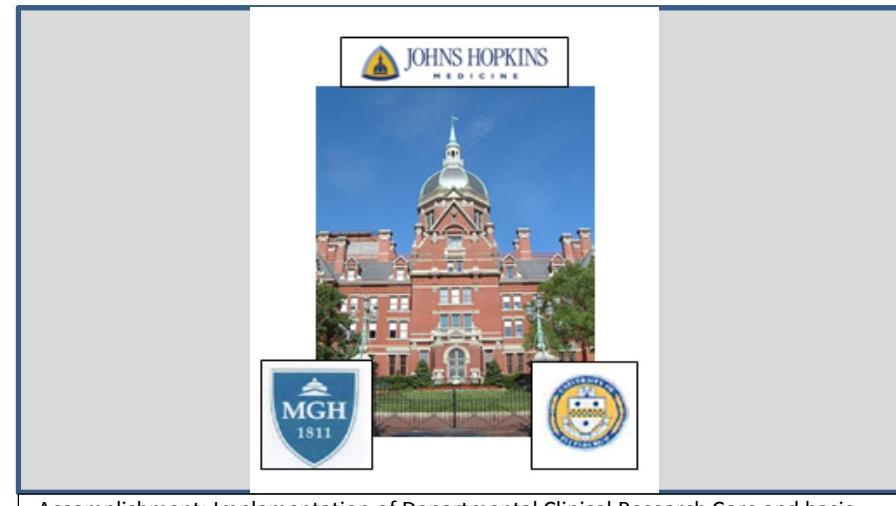


Study/Product Aim(s)

- Establishing monthly contact with sites during Year 1 of grant to facilitate communication and annual report generation.
- Continuing monthly contact with sites during Year 2 of grant to facilitate communication and annual report generation.
- Continuing monthly contact with sites during Year 3 of grant to facilitate communication and final report generation.

Approach

The purpose of this administrative core is to coordinate the efforts of the collaborating sites in order to ensure timely meeting of project aims and milestones while facilitating site communications with the sponsor.



Accomplishment: Implementation of Departmental Clinical Research Core and basic sciences support to enable intra- and inter-institutional research collaborations and perform grant management for both commercial and federal sponsors.

Timeline and Cost

Activities	CY	14	15	16
Establishing monthly contact with sites during Year 1 of grant to facilitate communication and annual report generation				
Continuing monthly contact with sites during Year 2 of grant to facilitate communication and annual report generation				
Continuing monthly contact with sites during Year 3 of grant to facilitate communication and final report generation.				
Estimated Budget (\$K)	\$93,790	\$95,558	\$96,950	

Goals/Milestones

CY14 Goals

- ✓ Collect & Review Consortium Quarterly Reports
- ✓ Conference Calls with Consortium Sites
- Milestone: Local IRB/IACUC Approval & HRPO/ACURO Approval

CY15 Goals

- ✓ Collect & Review Consortium Quarterly Reports
- ✓ Conference Calls with Consortium Sites
- ✓ Milestone: Local IRB/IACUC Continuing Review Approval
- ✓ Milestone: HRPO/ACURO Continuing Review Approval

CY16 Goals

- Collect & Review Consortium Quarterly Reports
- Conference Calls with Consortium Sites
- Complete and submit final Consortium Report to Sponsor
- ✓ Milestone: Local IRB/IACUC Continuing Review Approval
- Milestone: HRPO/ACURO Continuing Review Approval

Comments/Challenges/Issues/Concerns

- N/A

Budget Expenditure to Date

Projected Expenditure: N/A

Actual Expenditure: \$241,867

Updated: October 15, 2016